REMARKS/ARGUMENTS

The Claims

Claims 82-92 are currently pending in the application.

Rejection under 35 U.S.C. 102

The rejection of Claims 82-92 under 35 U.S.C. 102(e) as being anticipated by Gorman *et al.* (U.S. Patent No. 6,242,586, hereafter the "'586 patent") has been maintained in the present office action.

The Examiner argues that the '586 patent anticipates the claimed invention because it allegedly teaches antibodies which bind to human OPGbp and inhibit osteoclast formation. In particular, it is alleged that the '586 patent disclosure of an antibody to murine 499E9 (OPGbp)[1] is sufficient for anticipation because the patent: 1) discloses that their invention is not limited to a mouse embodiment (citing lines 44-50 of column 9); and 2) explicitly teaches that antibodies to mouse OPGbp will crossreact with OPGbp from other species (citing particularly example 4).

"A claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference" *Celeritas Techs. Ltd v. Rockwell Int'l Corp.* 47 USPQ2d 1516, 1522 (Fed. Cir. 1998). A prior art reference may anticipate even when claim limitations are not expressly found in that reference, but are nonetheless inherent in it. See e.g., *Atlas Powder Co. v. IRECO Inc.*, 51 USPQ2d 1943 (Fed. Cir. 1999); *Titanium Metals Corp. v. Banner* 227 USPQ 773 (Fed. Cir. 1985). "Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich* 212 USPQ 323, 326 (CCPA 1981). In addition, a prior art reference which anticipates must be enabling so that the claimed subject matter may be made or used by one of ordinary skill in the art. See, for example *Elan Pharm., Inc. v. Mayo Found.*

[1] The murine protein termed "499E9" in the '586 patent has an amino acid sequence identical to murine OPGbp in the present application. Thus, the terms "499E9" and OPGbp are used interchangeably with respect to the murine protein.

68 USPQ2d 1373 (Fed. Cir. 2003), restating previous holdings that in order to anticipate, a reference must provide sufficient disclosure to enable those skilled in the art to make the claimed invention without undue experimentation.

It is believed that the bases for the Examiner's rejection as set forth above fail on both legal and scientific grounds. Claim 82 recites in part "a human monoclonal antibody or fragment thereof which binds specifically to an osteoprotegerin binding protein of SEQ ID NO:39 [human OPGbp] ..." and accordingly the '586 patent must expressly or inherently disclose such an antibody. The '586 patent does not expressly disclose human OPGbp having the amino acid sequence of SEQ ID NO:39 and therefore does not disclose every limitation of Claim 82. The Examiner relies on the disclosure at column 9, lines 44-50 of the '586 patent which states in part:

> The embodiment [of 499E9 or OPGbp] characterized herein is from mouse, but other primate, e.g., human, variants will exist. Additional sequences for proteins in other mammalian species, e.g., primates and rodents, will also be available.

The above description does not provide an adequate written description of human 499E9 (OPGbp) as no structural information for human 499E9 has been set forth. *Regents of the University of California v. Eli Lilly & Co.* 43 USPQ2d 1398 (Fed. Cir. 1997). It is well established that the mere statement that the invention encompasses other embodiments does not establish possession of such embodiments. Thus, the statement that other embodiments of the murine protein, such as a human form, are contemplated does not confer possession of the human protein.

The Examiner also refers to Example 4 as evidence of a teaching that antibodies to murine OPGbp will cross-react with OPGbp from other species. The relevant section reads as follows (col. 27, lines 51-53):

> Alternatively, antibodies raised against mouse 499E9 will be used to screen for cells which express cross-reactive protein from an appropriate, e.g., cDNA library.

According to the specification, antibodies raised against mouse 499E9 are used to screen for any cross-reactive protein. There is nothing in the '586 specification which indicates that such a screening would even result in the identification of a cross-reactive protein or what the cross-reactive protein might be. No evidence has been presented to suggest that screening with an anti-murine 499E9 antibody would necessarily and without fail identify

human OPGbp as a cross-reactive protein. The specification fails to provide an express or inherent disclosure of antibodies which bind specifically to human OPGbp.

The Examiner further argues that the 84.1% identity between the amino acid sequences of human and murine OPGbp and the ability of antibodies to cross-react with both human and murine forms of a protein suggest that anti-murine 499E9 antibodies in the '586 patent anticipate the presently claimed antibodies. The Examiner has not provided any evidence that a cross-reacting antibody of the kind allegedly described in the '586 patent would "specifically bind" human OPGbp as set forth in Claim 82 and claims depending therefrom. In fact, the '586 patent provides in Example 5 a method for preparing antibodies "specific for 499E9". Thus, the patent only teaches methods for making antibodies that are specific for murine OPGbp and not for human OPGbp.

It has been previously argued that, because of the high degree of similarity in amino acid sequences between murine and human OPGbp, it would be "reasonable" for antibodies which specifically bind murine OPGbp to also bind, or cross-react with, human OPGbp. However, for the '586 patent to anticipate the claimed subject matter, cross-reacting anti-murine OPGbp antibodies must be observed necessarily and without fail and not simply be a "reasonable occurrence". There is no credible evidence that cross-reacting antibodies would necessarily occur. Notwithstanding this, as stated above, the mere existence of cross-reacting antibodies does not mean that such antibodies specifically bind human OPGbp as set forth in Claim 82.

In summary, the Examiner has failed to establish a *prima facie* case of anticipation based on the teachings of the '586 patent and the rejection should be withdrawn.

Rejection under 35 U.S.C. 103

Claims 82-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,740,522 to Anderson (hereafter the "'522 patent") in view of PCT publication no. WO93/12227, both references having been disclosed by Applicant).

The Examiner argues that the '522 patent discloses antibodies that bind RANKL and their methods of use. The '522 patent is also said to disclose RANKL antibodies which inhibit signaling to RANK and pharmaceutical compositions comprising the antibodies. These teachings are said to differ from the present invention in that the antibodies are not

disclosed as being human antibodies. WO93/12227 is said to disclose methods of making human monoclonal antibodies for use in various treatment methods with the advantage that human antibodies would be less immunogenic than murine antibodies. The Examiner also argues that antibodies binding the BB' and EF loops of human OPGbp (as recited in Claims 86 and 87) would be obvious in view of the disclosure in the '522 patent of antibodies which block RANKL signaling.

Applicant maintains that the claimed antibodies are not obvious as they exhibit surprising and unexpected properties, namely that human monoclonal antibodies which are raised against and bind with high affinity to human OPGbp and inhibit osteoclast formation do not exhibit any detectable binding to murine OPGbp and therefore have no effect on the activity of murine OPGbp. Such antibodies are described in WO 01/62932 ("AT antibody, see Figure 30 and p. 110, starting on line 10), WO 03/002713 ("alpha OPGL-1", see Table 4, p. 96); and WO 03/086289 (antibodies "9H7, 18B2, 2D8, 2E11, 16E1 and 22B3", see Table 5, p. 64). Thus, even given the high degree of similarity of murine and human OPGbp (84.1% identity in amino acid sequence), human antibodies which are highly active in binding human OPGbp and inhibiting osteoclast formation do not recognize murine OPGbp. This high degree of specificity means that human antibodies to human OPGbp are less likely to recognize non-target molecules than antibodies that show a greater tendency to cross-react.. This specificity reduces the likelihood that an antibody therapeutic, when administered to a patient, would interact with a molecule unrelated to the target and trigger an adverse event.

In view of the evidence related to surprising and unexpected results, Applicant maintains that the claimed invention is non-obvious over the cited references.

Rejection for obviousness-type double patenting

Claims 82-92 stand provisionally rejected under obviousness-type double patenting over Claims 2-9, 21 and 22 of co-pending U.S. Serial No. 10/180,648 (hereafter the "'648 application"), over Claims 1-50, 52 and 53-73 of co-pending U.S. Serial No. 10/408,901 (hereafter the "'901 application"), and over Claims 10-53 of co-pending U.S. Serial No. 09/791,153 (hereafter the "'153 application") in view of WO 93/12227 (made of record by Applicant). The claims of the '648, '901 and '153 applications and the arguments by the Examiner related thereto have been described in the prior response dated May 9, 2007.

"Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly-owned patent when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by the patent" (MPEP section 804; *Eli Lilly & Co. v. Barr Labs., Inc.* 58 USPQ2d 1869 (Fed. Cir. 2001). A claim under examination is rejected as being not patentably distinct where it is anticipated by, or would have been obvious over, a claim in a separate application or patent, where the application(s) or patent(s) must have at least one common inventor and/or be commonly owned or assigned.

Applicant has pointed out that the '648, '901 and '153 applications cited in this rejection have priority dates of June 26, 2001, April 5, 2002 and February 23, 2000, respectively, all of which are later than the April 16, 1997 priority date of the present application. Since later filed disclosures claiming antibody species cannot anticipate or render obvious an earlier filed and claimed antibody genus encompassing the species, none of the claims the cited applications can be used to anticipate or render obvious any of the present claims. In addition, issuance of the present application as a patent would not unjustly extend the term of exclusion since such a patent would have an expiration date earlier than any patent which would issue from any of the '648, '901 and '153 applications. Finally, Examiner has previously acknowledged that the failure to file a terminal disclaimer would not affect the allowance of the claims provided all other rejections related to patentability have been overcome.

The Examiner has maintained the rejection "because applicant may always submit a petition for an unintentional delay in a claim for priority and thus the filing dates for the aforementioned co-pending applications could change" (Office Action at p. 8). While Applicant could in principle file such a petition to claim earlier priority dates for one or more of the co-pending '648, '901 and '153 applications, such a petition, if granted, would have no bearing on the obviousness-type double patenting rejection since the co-pending applications would still not have an earlier priority date than the present application and therefore would not expire sooner than the present application. The filing of a terminal disclaimer in this instance would not change the expiration date of a patent issued from the present application. Accordingly, it is requested that the rejection be withdrawn.

CONCLUSION

Claims 82-92 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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